10523843

http://www.cas.org/support/stngen/stndoc/properties.html

```
=> s threo DOPS
         39976 THREO
             8 DOPS
L1           2 THREO DOPS
                (THREO(W)DOPS)

=> d l1

L1   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2008 ACS on STN
RN   23651-95-8  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   L-Tyrosine, β,3-dihydroxy-, (βR)-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   L-Tyrosine, β,3-dihydroxy-, threo-
CN   Serine, 3-(3,4-dihydroxyphenyl)-, L-threo- (8CI)
OTHER NAMES:
CN   (-)-threo-3,4-Dihydroxyphenylserine
CN   DOPS
CN   Droxidopa
CN   L-DOPS
CN   L-threo-β-(3,4-Dihydroxyphenyl)serine
CN   L-threo-3,4-Dihydroxyphenylserine
CN   L-threo-3-(3,4-Dihydroxyphenyl)serine
CN   L-threo-DOPS
CN   L-Threodops
CN   SM 5688
CN   threo-Dopaserine
FS   STEREOSEARCH
MF   C9 H11 N O5
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, BEILSTEIN*, BIOSIS, BIOTECHNO, CA,
       CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE,
       IFICDB, IFIPAT, IFIUDB, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA,
       MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER,
       USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO

Absolute stereochemistry.  Rotation (-).
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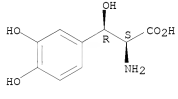


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             218 REFERENCES IN FILE CA (1907 TO DATE)
               7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             219 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> d l1 2-2
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L1   ANSWER 2 OF 2  REGISTRY  COPYRIGHT 2008 ACS on STN
RN   3916-18-5  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   D-Tyrosine, β,3-dihydroxy-, (βS)-rel- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   DL-Tyrosine, β,3-dihydroxy-, threo-
CN   Serine, 3-(3,4-dihydroxyphenyl)-, DL-threo- (8CI)
OTHER NAMES:
CN   DL-threo-3,4-Dihydroxyphenylserine
CN   DL-threo-Dihydroxyphenylserine
CN   DL-threo-DOPS
CN   threo-2-Amino-3-(3,4-dihydroxyphenyl)-3-hydroxypropionic acid
FS   STEREOSEARCH
DR   6204-89-3, 43160-12-9
MF   C9 H11 N O5
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS,
       CASREACT, CHEMCATS, CHEMLIST, CSCHEM, IFICDB, IFIPAT, IFIUDB, IPA,
       RTECS*, TOXCENTER, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**
         (**Enter CHEMLIST File for up-to-date regulatory information)

Relative stereochemistry.
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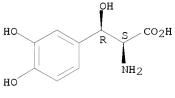


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             110 REFERENCES IN FILE CA (1907 TO DATE)
               2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             110 REFERENCES IN FILE CAPLUS (1907 TO DATE)
               1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)


=> file MEDICINE
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    14.76      14.97

FILE 'ADISCTI' ENTERED AT 12:26:39 ON 01 OCT 2008
COPYRIGHT (C) 2008 Adis Data Information BV

FILE 'ADISINSIGHT' ENTERED AT 12:26:39 ON 01 OCT 2008
COPYRIGHT (C) 2008 Adis Data Information BV

FILE 'ADISNEWS' ENTERED AT 12:26:39 ON 01 OCT 2008
COPYRIGHT (C) 2008 Adis Data Information BV
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FILE 'BIOSIS' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'BIOTECHNO' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'CAPLUS' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'DDFB' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'DDFU' ACCESS NOT AUTHORIZED

FILE 'DGENE' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'DISSABS' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'DRUGB' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'DRUGMONOG2' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'DRUGU' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'EMBAL' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'EMBASE' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'ESBIOBASE' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'IFIPAT' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'IMSDRUGNEWS' ENTERED AT 12:26:39 ON 01 OCT 2008

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FILE 'IPA' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'KOSMET' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'LIFESCI' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'MEDLINE' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'NAPRALERT' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'NLDB' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'NUTRACEUT' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'PASCAL' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'PCTGEN' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'PHARMAML' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'PHIC' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'PHIN' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'SCISEARCH' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'TOXCENTER' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'USGENE' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'USPATFULL' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'USPATOLD' ENTERED AT 12:26:39 ON 01 OCT 2008

FILE 'USPAT2' ENTERED AT 12:26:39 ON 01 OCT 2008

=> s l1 or threo DOPS or droxidopa
L2 1889 L1 OR THREO DOPS OR DROXIDOPA

=> s headache or migraine or tension or premenstrual or PMS
L3 2370013 HEADACHE OR MIGRAINE OR TENSION OR PREMENSTRUAL OR PMS

=> s l2 and l3
L4 111 L2 AND L3

=> s premenstrual headache
L5 21 PREMENSTRUAL HEADACHE

```
=> s tension headache
L6         9857 TENSION HEADACHE

=> s migraine
L7       184142 MIGRAINE

=> s headache
L8       368794 HEADACHE

=> s l5 or l6 or l7 or l8
L9       472840 L5 OR L6 OR L7 OR L8

=> s l4 and
MISSING TERM AFTER L4 AND
Operators must be followed by a search term, L-number, or query name.

=> s l4 and l9
L10           86 L4 AND L9

=> s l10 and PD<2002
   6 FILES SEARCHED...
'2002' NOT A VALID FIELD CODE
'2002' NOT A VALID FIELD CODE
'2002' NOT A VALID FIELD CODE
  15 FILES SEARCHED...
'2002' NOT A VALID FIELD CODE
  22 FILES SEARCHED...
'2002' NOT A VALID FIELD CODE
'2002' NOT A VALID FIELD CODE
  29 FILES SEARCHED...
'2002' NOT A VALID FIELD CODE
  32 FILES SEARCHED...
L11           15 L10 AND PD<2002

=> dup rem
ENTER L# LIST OR (END):l11
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGMONOG2,
IMSPRODUCT, KOSMET, NUTRACEUT, PCTGEN, PHARMAML, USGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L11
L12            12 DUP REM L11 (3 DUPLICATES REMOVED)

=> d l12 1-12 ibib, kwic

L12  ANSWER 1 OF 12  USPATFULL on STN
ACCESSION NUMBER:       2001:205909  USPATFULL
TITLE:                  Polymorphic form of a tachykinin receptor antagonist
INVENTOR(S):            Crocker, Louis, Belle Mead, NJ, United States
                        Mccauley, James, Belle Mead, NJ, United States
PATENT ASSIGNEE(S):     Merck & Co., Inc. (U.S. corporation)

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 20010041702     A1   20011115            <--
                        US 6432953         B2   20020813
APPLICATION INFO.:      US 2001-850370     A1   20010507  (9)
RELATED APPLN. INFO.:   Division of Ser. No. US 1999-458168, filed on 9 Dec
                        1999, GRANTED, Pat. No. US 6229010

                               NUMBER        DATE
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PRIORITY INFORMATION:	US 1997-51600P 19970702 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	J. ERIC THIES, Patent Department, Merck & Co., Inc, P.O. Box 2000, Rahway, NJ, 07065-0907
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Page(s)
LINE COUNT:	2079

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . tachykinin receptor antagonist useful in the treatment or prevention of disorders of the central nervous system, inflammatory diseases, pain or migraine, asthma, and emesis. The instant polymorphic form has advantages over the other known forms of 2-(R)-(1-(R)-(3,1-bis(trifluoro-methyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine in terms of thermodynamic. . .

SUMM . . . antagonist useful in the in the treatment or prevention of disorders of the central nervous system, inflammatory diseases, pain or migraine, asthma, and emesis.

SUMM [0007] Evidence has been reviewed for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory. . .

DETD [0015] and is a tachykinin receptor antagonist useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis.

DETD . . . the novel polymorphic form of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, is a tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis. Accordingly, the present invention is further concerned with pharmaceutical formulations comprising this polymorphic form as an active. . .

DETD . . . particular substance P and neurokinin A in the treatment of gastrointestinal disorders, central nervous system disorders, inflammatory diseases, pain or migraine, asthma, and emesis in a mammal in need of such treatment. This activity may be demonstrated by the following assay.

DETD . . . and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, . . .

DETD . . . chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intercranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, . . .

DETD . . . such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

DETD . . . emesis, including acute, delayed or anticipatory emesis, such

as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compound of the present invention is of use in the treatment of. . .

DETD . . . such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteroarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain. The present invention further provides the compound of the present invention for use in. . .

DETD [0068] It will be appreciated that for the treatment or prevention of migraine, the compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT.sub.l agonists, especially sumatriptan or rizatriptan. Likewise, for the treatment of behavioural hyperalgesia, the compound. . .

DETD . . . azamianserin, bazinaprine, fefuraline, bifemelane, binodaline, bipenamol, brofaromine, bupropion, caroxazone, cericlamine, cianopramine, cimoxatone, citalopram, clemeprol, clovoxamine, dasepinil, deanol, demexiptiline, dibenzepin, dothiepin, droxidopa, enefexine, setazolam, etoperidone, femoxetine, fengabine, fezolamine, fluotracen, idazoxan, indalpine, indeloxazine, iprindole, levoprotiline, litoxetine, lofepramine, medifoxamine, metapramine, metralindole, mianserin, milnacipran, minaprine,. . .

L12 ANSWER 2 OF 12 USPATFULL on STN

ACCESSION NUMBER:	2001:67821 USPATFULL
TITLE:	Polymorphic form of a tachykinin receptor antagonist
INVENTOR(S):	Crocker, Louis, Belle Mead, NJ, United States McCauley, James, Belle Mead, NJ, United States
PATENT ASSIGNEE(S):	Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6229010	B1	20010508	<--
APPLICATION INFO.:	US 1999-458168		19991209 (9)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1998-212511, filed on 15 Dec 1998, now patented, Pat. No. US 6096742			

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-51600P	19970702 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Reamer, James H.
LEGAL REPRESENTATIVE:	Thies, J. Eric, Rose, David L.
NUMBER OF CLAIMS:	7
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT:	2023

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . tachykinin receptor antagonist useful in the treatment or prevention of disorders of the central nervous system, inflammatory diseases, pain or migraine, asthma, and emesis. The instant polymorphic form has advantages over the other known forms of 2-(R)-(1-(R)-(3,,5-bis(trifluoro-methyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine in terms

of thermodynamic. . .

SUMM . . . antagonist useful in the in the treatment or prevention of disorders of the central nervous system, inflammatory diseases, pain or migraine, asthma, and emesis.

SUMM Evidence has been reviewed for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory. . .

DETD and is a tachykinin receptor antagonist usefuil in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis.

DETD . . . . the novel polymorphic form of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, is a tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis. Accordingly, the present invention is further concerned with pharmaceutical formulations comprising this polymorphic form as an active. . .

DETD . . . particular substance P and neurokinin A in the treatment of gastrointestinal disorders, central nervous system disorders, inflammatory diseases, pain or migraine, asthma, and emesis in a mammal in need of such treatment. This activity may be demonstrated by the following assay.

DETD . . . and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example,. . .

DETD . . . chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intercranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation,. . .

DETD . . . such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

DETD . . . emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compound of the present invention is of use in the treatment of. . .

DETD . . . such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteroarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain. The present invention further provides the compound of the present invention for use in. . .

DETD It will be appreciated that for the treatment or prevention of migraine, the compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT.sub.1 agonists, especially sumatriptan or rizatriptan. Likewise, for the treatment of behavioural hyperalgesia, the compound. . .

DETD . . . azamianserin, bazinaprine, fefuraline, bifemelane, binodaline, bipenamol, brofaromine, bupropion, caroxazone, cericlamine,

cianopramine, cimoxatone, citalopram, clemeprol, clovoxamine, dasepinil, deanol, demexiptiline, dibenzepin, dothiepin, droxidopa, enefexine, setazolam, etoperidone, femoxetine, fengabine, fezolamine, fluotracen, idazoxan, indalpine, indeloxazine, iprindole, levoprotiline, litoxetine, lofepramine, medifoxamine, metapramine, metralindole, mianserin, milnacipran, minaprine,. . .

L12 ANSWER 3 OF 12 USPATFULL on STN

ACCESSION NUMBER:	2000:98427 USPATFULL
TITLE:	Polymorphic form of a tachykinin receptor antagonist
INVENTOR(S):	Crocker, Louis, Belle Mead, NJ, United States McCauley, James, Belle Mead, NJ, United States
PATENT ASSIGNEE(S):	Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6096742		20000801	<--
APPLICATION INFO.:	US 1998-212511		19981215 (9)	
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-108567, filed on 1 Jul 1998, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Reamer, James H.			
LEGAL REPRESENTATIVE:	Thies, J. Eric, Rose, David L.			
NUMBER OF CLAIMS:	8			
EXEMPLARY CLAIM:	1,3			
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)			
LINE COUNT:	2018			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . tachykinin receptor antagonist useful in the treatment or prevention of disorders of the central nervous system, inflammatory diseases, pain or migraine, asthma, and emesis. The instant polymorphic form has advantages over the other known forms of 2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine in terms of thermodynamic. . .

SUMM . . . antagonist useful in the in the treatment or prevention of disorders of the central nervous system, inflammatory diseases, pain or migraine, asthma, and emesis.

SUMM Evidence has been reviewed for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory. . . .

DETD . . . 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine has the structure: ##STR1## and is a tachykinin receptor antagonist useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis.

DETD . . . the novel polymorphic form of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, is a tachykinin receptor antagonists useful in the treatment of inflammatory diseases, pain or migraine, asthma, and emesis. Accordingly, the present invention is further concerned with pharmaceutical formulations comprising this polymorphic form as an active. . .

DETD . . . particular substance P and neurokinin A in the treatment of gastrointestinal disorders, central nervous system disorders,

inflammatory diseases, pain or migraine, asthma, and emesis in a mammal in need of such treatment. This activity may be demonstrated by the following assay.

DETD . . . and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example,. . .

DETD . . . chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intercranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation,. . .

DETD . . . such as scleroderma and eosinophilic fasciolisis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

DETD . . . emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compound of the present invention is of use in the treatment of. . .

DETD . . . such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteroarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain. The present invention further provides the compound of the present invention for use in. . .

DETD It will be appreciated that for the treatment or prevention of migraine, the compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT.sub.1 agonists, especially sumatriptan or rizatriptan. Likewise, for the treatment of behavioural hyperalgesia, the compound. . .

DETD . . . azamianserin, bazinaprine, fefuraline, bifemelane, binodaline, bipenamol, brofaromine, bupropion, caroxazone, cericlamine, cianopramine, cimoxatone, citalopram, clemeprol, clovoxamine, dasepinil, deanol, demexiptiline, dibenzepin, dothiepin, droxidopa, enefexine, setazolam, etoperidone, femoxetine, fengabine, fezolamine, fluotracen, idazoxan, indalpine, indeloxazine, iprindole, levoprotiline, litoxetine, lofepramine, medifoxamine, metapramine, metralindole, mianserin, milnacipran, minaprine,. . .

L12 ANSWER 4 OF 12 USPATFULL on STN

ACCESSION NUMBER:	1998:17360 USPATFULL
TITLE:	Compositions and methods for topical administration of pharmaceutically active agents
INVENTOR(S):	Kanios, David P., Miami, FL, United States Gentile, Joseph A., Plantation, FL, United States Mantelle, Juan A., Miami, FL, United States Sablotsky, Steven, Miami, FL, United States
PATENT ASSIGNEE(S):	Noven Pharmaceuticals, Inc., Miami, FL, United States (U.S. corporation)

NUMBER	KIND	DATE

PATENT INFORMATION: US 5719197 19980217 <--
APPLICATION INFO.: US 1995-477361 19950607 (8)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-112330, filed on 27 Aug 1993, now patented, Pat. No. US 5446070 which is a continuation-in-part of Ser. No. US 1991-813196, filed on 23 Dec 1991, now patented, Pat. No. US 5234957 which is a continuation-in-part of Ser. No. US 1991-661827, filed on 27 Feb 1991, now abandoned , said Ser. No. US 1995-477361, filed on 7 Jun 1995 which is a continuation-in-part of Ser. No. US 1993-67001, filed on 26 May 1993 which is a continuation of Ser. No. US 1991-671709, filed on 2 Apr 1991, now patented, Pat. No. US 5300291 which is a continuation-in-part of Ser. No. US 1989-295847, filed on 11 Jan 1989, now patented, Pat. No. US 4994267 which is a continuation-in-part of Ser. No. US 1988-164482, filed on 4 Mar 1988, now patented, Pat. No. US 4814168
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Azpuru, Carlos A.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
LINE COUNT: 1799
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD ANTIPARKINSONIAN such as Amantadine, Benserazide, Bietanautine, Biperiden, Budipine, Carbidopa, Deprenyl, Dexetimide, Diethazine, Droxidopa, Ethopropazine, Ethylbenzhydramine, Levodopa, Piroheptine, Pridinol, Prodipine, Terguride, Tiapride, Tigloidine
CLM What is claimed:
. . . or muscarinic cholinergic blocking drugs, mydriatics, psychic energizers, humoral agents, antispasmodic drugs, antidepressants, antidiabetics, anorexic drugs, anti-allergic drugs, decongestants, antipyretics, anti-migraine drugs, antimalarial, antiulcer drugs, peptides, and anti-estrogens.

L12 ANSWER 5 OF 12 USPATFULL on STN
ACCESSION NUMBER: 97:27205 USPATFULL
TITLE: Threo-3-(3,4-dihydroxyphenyl)serine analgesic composition
INVENTOR(S): Takagi, Hiroshi, Kyoto, Japan
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Company, Limited, Osaka, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5616618		19970401	<--
	WO 9416689		19940804	<--
APPLICATION INFO.:	US 1995-495480		19950724	(8)
	WO 1994-JP120		19940128	
			19950724	PCT 371 date
			19950724	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1993-34366	19930129

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted

PRIMARY EXAMINER: Cook, Rebecca
LEGAL REPRESENTATIVE: Sughrue, Mion, Zinn, Macpeak & Seas
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 475
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . and chronic or continuous pains. Therefore, threo-3-(3,4-dihydroxyphenyl)serine is effective for the treatment of diseases with pains such as postoperative pain, headache, migraine, pains accompanied by rheumatism, post-herpes neuralgia, cancerous pain, pains associated with cervico-omo-brachial syndrome, shoulder periarthritis, spinal distortion, and spondylosis deformans.

SUMM The present invention relates to a medical use of threo-3-(3,4-dihydroxyphenyl)serine (hereinafter abbreviated as threo-DOPS). More particularly, the present invention relates to a medical use of threo-DOPS as an analgesic drug, especially in the treatment of acute and chronic pains or continuous pains.

SUMM . . . made extensive studies to achieve the foregoing object. As a result, it has been discovered that a pharmaceutical composition comprising threo-DOPS as an effective ingredient exhibits an analgesic activity to relieve chronic or continuous pain as well as acute pain. The. . .

SUMM That is, the present invention relates to an analgesic composition comprising as an effective ingredient threo-DOPS or a pharmaceutically acceptable acid addition salt thereof.

SUMM . . . relates to a method for the treatment of diseases with pains which comprises administering to human an effective dose of threo-DOPS or a pharmaceutically acceptable acid addition salt thereof.

SUMM The present invention further relates to use of threo-DOPS or a pharmaceutically acceptable acid addition salt thereof in the production of an analgesic composition.

DRWD FIG. 1 shows the results of the analgesic effect of L-threo-DOPS assessed by the tail flick method.

DRWD FIG. 2 shows the results of the analgesic effect of L-threo-DOPS assessed by the kaolin-induced writhing test.

DRWD FIG. 3 shows the results of the analgesic effect of L-threo-DOPS assessed by the formalin-induced encroachment test.

DRWD FIG. 4 shows the results of morphine antagonist, naloxone, on the analgesic effect of L-threo-DOPS assessed by the tail flick method and the kaolin-induced writhing test.

DRWD FIG. 5 shows the results of adrenaline blocking agent, phentolamine, on the analgesic effect of L-threo-DOPS assessed by the tail flick method.

DRWD FIG. 6 shows the results of decarboxylase inhibitor, benserazide, on the analgesic effect of L-threo-DOPS assessed by the tail flick method.

DRWD FIG. 7 shows the results of the analgesic effect of L-threo-DOPS by oral administration, which was assessed by the tail flick method.

DETD Threo-DOPS used in the present invention is a known compound represented by the following formula: ##STR1## This compound may be prepared according to known methods as reported in Japanese Patent Application KOKOKU No. 1-49139 and U.S. Pat. No. 4,480,109. Threo-DOPS has optically active L- and D-forms and racemic DL-form. Among them, L-threo-DOPS is

preferred for the purpose of the present invention. Since 1989, L-Threo-DOPS has been clinically applied to improve freezing gait observed in Parkinson's disease.

DETD In the present invention, threo-DOPS may be employed also in the form of pharmaceutically acceptable acid addition salts thereof. To form the acid addition salts,. . .

DETD According to the present invention, threo-DOPS or its pharmaceutically acceptable acid addition salts may also be used in combination with a decarboxylase inhibitor. Preferred examples of. . .

DETD It is known that, after administration, threo-DOPS is transported to a brain that is a site on which threo-DOPS acts, and then decarboxylated therein into a corresponding noradrenaline by decarboxylase to exhibit an activity for the treatment of Parkinson's disease (U.S. Pat. No. 4,497,826). It is also known that, where threo-DOPS is administered in combination with the decarboxylase inhibitor, decarboxylation of threo-DOPS by decarboxylase in the peripheral tissue can be prevented, resulting in that the transportation of threo-DOPS into a brain can be accelerated. As a result, a dose of threo-DOPS to be administered as a drug for treating Parkinson's disease may be reduced, and side effects of threo-DOPS in the peripheral tissue may be reduced (J. Pharm. Pharmacol., 1981, 33, 772-777).

DETD As will be noted from test examples described hereinafter, threo-DOPS in the present invention is also considered to be transported into a brain and converted therein into noradrenaline to exhibit an analgesic effect. It is thus expected in the present invention that the combination of threo-DOPS with decarboxylase inhibitors will reduce a dose of threo-DOPS as an analgesic, and will therefore prevent side effects in the peripheral tissue.

DETD Threo-DOPS or its pharmaceutically acceptable acid addition salt which is an effective ingredient of the present invention may be administered orally. . . dose in a conventional dosage form. Examples of preparations for oral administration include a tablet, capsule, syrup and suspension. Alternatively, threo-DOPS may also be administered parenterally in the dosage form of injection as a solution, emulsion or suspension.

DETD . . . by mixing the effective ingredient with a pharmaceutically acceptable and conventionally used carrier, excipient, binder, stabilizer and the like. Where threo-DOPS is administered in the dosage form of an injection, the composition may be formulated with a pharmaceutically acceptable buffer, solution aid, isotonic solution and the like. As pointed out hereinbefore, threo-DOPS has already been provided for clinical use, and those preparations may be, therefore, used as they are.

DETD Where threo-DOPS is administered in combination with a decarboxylase inhibitor, a kit comprising threo-DOPS or its pharmaceutically acceptable acid addition salt and a decarboxylase inhibitor is prepared and the thus prepared kit may be. . .

DETD A dose and dosage frequency of threo-DOPS or its pharmaceutically acceptable acid addition salt may vary depending upon the dosage form, conditions of disease to be treated,. . .

DETD . . . combination with the effective ingredient, it is sufficient to administer the inhibitor in a dose less than the dose of threo-DOPS by about 1/10.

DETD Threo-DOPS has an extremely weak toxicity, that is, LD.sub.50 is 10 g/kg or more when orally administered to mouse, and about. . .

DETD The analgesic composition of the present invention is effective for treating pains such as postoperative pain, headache, migraine, pains accompanied by rheumatism, post-herpes neuralgia, cancerous pain, pains associated with cervico-omo-brachial syndrome, shoulder periarthritis, spinal distortion, and spondylosis deformans.

DETD That is, it has been confirmed that the analgesic composition of the present invention comprising threo-DOPS as an effective ingredient has the effects set forth below, as will be noted from test examples hereinafter.

DETD . . . latency by administration of a drug (tail-flick test, see European Journal of Pharmacology, 212, 1992). The tail-flick test reveals that threo-DOPS exhibits the analgesic effect dose-dependently when subcutaneously administered to mice.

DETD . . . model for assessment of chronic pain is used [Pain, 51, 195-198 (1992)]. The analgesic effect was dose- dependently observed when threo-DOPS was administered subcutaneously and orally.

DETD (3) Mechanism of the Analgesic Effect of Threo-DOPS

DETD The analgesic effect of threo-DOPS is non-narcotic, because the effect was not antagonized by morphine antagonist, naloxone. Furthermore, the analgesic effect of threo-DOPS was suppressed by the administration of an adrenaline blocker, phentolamine, in the brain, and thus shown to act via adrenergic nerve in the brain. Such pharmacological properties of threo-DOPS are quite dissimilar to those of conventional analgesics.

DETD These results reveal that threo-DOPS or pharmaceutically acceptable acid addition salt thereof used in the present invention have a mechanism different from that of known. . .

DETD Antinociceptive tests for L-threo-DOPS

DETD L-Threo-DOPS was suspended in a 0.2% Tween 80 solution and the resulting suspension was subcutaneously administered in a dose of 100. . .

DETD . . . shown in FIG. 1. The left graph in FIG. 1 shows latency with passage of time after subcutaneous administration of L-threo-DOPS in a dose of 400 mg/kg according to the tail flick test. In the left graph, the symbol .largecircle. denotes the group administered with vehicle only (n=8), and the symbol .circle-solid. denotes the group administered with L-threo-DOPS (n=5). The right graph in FIG. 1 shows a relationship between the dose of L-threo-DOPS administered and latency (second) one hour after administration of L-threo-DOPS. In the right graph, the symbol V denotes the group administered with vehicle only. *P<0.05, **P<0.01 (when compared to the. . .

DETD As is seen from FIG. 1, 40 or more minutes after administration of L-threo-DOPS in a dose of 400 mg/kg, a significantly prolonged latency was observed, and reached the maximum latency one hour after. . . . was gradually recovered, and no significant effect was observed 2 hours later (see the left graph). The antinociceptive action of L-threo-DOPS, 60 minutes after administration, was dose-dependent in the range of 100 to 400 mg/kg (see the right graph).

DETD Thirty minutes, 1 hour and 2 hours before administration of kaolin, L-threo-DOPS was subcutaneously administered in a dose ranging from 100 to 400 mg/kg.

DETD . . . FIG. 2. The left graph in FIG. 2 shows the total count of writhing reactions with passage of time, after L-threo-DOPS was subcutaneously administered in a dose of 200 mg/kg according to the kaolin-induced writhing method. In the left graph, the symbol .largecircle. denotes the group administered with vehicle only, and the symbol .circle-solid. denotes the group administered with L-

threo-DOPS. The right graph in FIG. 2 shows a relationship between the dose of L-threo-DOPS administered and the total count of writhing reactions one hour after administration of L-threo-DOPS. The symbol V denotes the group administered with vehicle only (n=5). **P<0.01, ***P<0.001 (when compared to the group administered with. . .

DETD As is seen from FIG. 2, after administration of L-threo-DOPS in a dose of 200 mg/kg, the count of kaolin-induced writhing response decreased to the half, indicating a significant antinociceptive action. The decreasing tendency was also observed 30 minutes and 2 hours after administration of L-threo-DOPS, but the observed decrease was insignificant (see the left graph). The effect which was observed 60 minutes after administration of L-threo-DOPS was dose-dependent in the range of 100 to 400 mg/kg (see the right graph).

DETD Fifty minutes before the formalin administration, L-threo-DOPS was subcutaneously administered in a dose ranging from 100 to 200 mg/kg.

DETD . . . times required for licking and biting (second) for Phase I (0-5 minutes after the formalin administration) and the dose of L-threo-DOPS administered. The right graph in FIG. 3 shows in the formalin-induced nociceptive test (n=9-11) a relationship between the times required for licking and biting (second) for Phase II (10-30 minutes after the formalin administration) and the dose of L-threo-DOPS administered. The symbol V denotes the group administered with vehicle only. *P<0.05 (as compared to the group administered with vehicle. . .

DETD As is seen from FIG. 3, subcutaneous administration of L-threo-DOPS in a dose of 100 to 200 mg/kg did not affect the time required for the nociceptive reaction for Phase. . . inhibited the reaction for Phase II (the right graph). While not shown in the graphs, even though the dose of L-threo-DOPS was increased to 400 mg/kg, no better effect was obtained.

DETD Antagonistic Effect of L-threo-DOPS Antinociceptive Action on Naloxone (Morphine Antagonist)

DETD . . . tail flick test method, however, 1 mg/kg of naloxone was subcutaneously administered 40 minutes after administration of 400 mg/kg of L-threo-DOPS, and the latency was measured 60 minutes after the 400 mg/kg L-threo-DOPS administration. The obtained data are shown in terms of change in latency (Δ latency). In the kaolin-induced writhing test, 0.01 mg/kg of naloxone was subcutaneously administered 55 minutes after administration of 400 mg/kg of L-threo-DOPS, and kaolin was administered 5 minutes after the administration of naloxone.

DETD . . . FIG. 4. The left graph in FIG. 4 shows change in latency (Δ latency (second)) 60 minutes after administration of L-threo-DOPS according to the tail flick method (n=1). The right graph in FIG. 4 shows the total count of writhing reactions 60 minutes after administration of L-threo-DOPS according to the kaolin-induced writhing test (n=4 or 5). The symbol V denotes the group administered with vehicle only, and. . .

DETD As is seen from FIG. 4, the antinociceptive action of L-threo-DOPS in the tail flick test and the kaolin-induced writhing test was hardly affected by morphine antagonist, naloxone (Nlx). This reveals that the action of L-threo-DOPS is non-narcotic analgesic activity.

DETD Effect of Phentolamine as an α-Adrenaline Receptor Blocker on the Antinociceptive Action of L-threo-DOPS

DETD Phentolamine was administered intracerebral-ventricularly (i.c.v.) or intrathecaly (i.th.) in a dose of 0.1 to 1 μg/mouse, 40 minutes after

L-threo-DOPS was administered in a dose of 400 mg/kg. Then, the effect of phentolamine against L-threo-DOPS-induced antinociceptive action was determined in the tail flick test.

DETD . . . shown in FIG. 5. The results in FIG. 5 indicates change in latency (Δ latency, second) 60 minutes after the L- threo -DOPS administration. The left graph in FIG. 5 shows the effect of phentolamine when intracerebralventricularly (i.c.v.) administered, and the right graph. . .

DETD . . . phentolamine itself did not affect the latency. However, phentolamine almost completely inhibited prolongation of the latency by subcutaneous administration of L-threo-DOPS in a dose of 400 mg/kg (see the left graph). This effect by phentolamine was also observed even at a. . . μg/mouse. On the other hand, when phentolamine was intracerebralventricularly administered in a dose of 1 μg/mouse, the antinociceptive action of L- threo-DOPS (400 mg/kg, s.c.) was partially but significantly inhibited (see the right graph).

DETD The results shown in Test Examples 1 through 3 reveal that L-threo-DOPS exhibits a non-opiate type antinociceptive action by systemic administration. It is also suggested that noradrenergic system in the brain and. . .

DETD Effect of Benserazide (Peripheral Nerve Decarboxylase Inhibitor) on the Antinociceptive Action of L-threo-DOPS

DETD Benserazide was administered subcutaneously in a dose of 1 mg/kg, 60 minutes before the subcutainious administration of L-threo-DOPS (400 mg/kg). Alternatively, benserazide was administered intracerebralventricularly at a dose of 25 μg/mouse, 30 minutes before L-threo-DOPS was subcutaneously administered in a dose of 400 mg/kg. The effect of benserazide on the L-threo -DOPS-induced antinociceptive action 60 minutes after the L-threo-DOPS administration was examined according to the tail flick test.

DETD . . . shown in FIG. 6. The results in FIG. 6 indicate change in latency (Δ latency, second) 60 minutes after the L- threo -DOPS administration. The left graph in FIG. 6 shows the effect of benserazide when subcutaneously administered, and the right graph in. . .

DETD . . . as a peripheral decarboxylase inhibitor was administered subcutaneously, BSZ did not give any significant effect on the antinociceptive action of L-threo-DOPS (see the left graph). However, when benserazide was administered intracerebralventricularly, the antinociceptive action of L-threo-DOPS was potently inhibited (see the right graph).

DETD The forgoing results suggest that L-threo-DOPS would be transported into the central nervous system (brain and spinal code) after systemic administration, and decarboxylated therein by decarboxylase. . .

DETD Antinociceptive Action of L-threo-DOPS by Oral Administration

DETD L-Threo-DOPS was orally administered to mice in doses of 200, 400 and 800 mg/kg, and was examined for the antinociceptive action. . .

DETD . . . in FIG. 7. The results in FIG. 7 indicate, in the tail flick test, a relationship between the dose of L-threo-DOPS when orally administered and change in latency (Δ latency, second) 60 minutes after the L-threo-DOPS administration (n=6). *P<0.05, **P<0.01 (as compared to the control group).

DETD As is seen from FIG. 7, L-threo-DOPS shows the

antinociceptive action dose-dependently when orally administered in the range of 200 to 800 mg/kg. In all cases, a. . . . administration, and reached the maximum level 60 minutes after the administration. Then, the effect gradually decreased. The results establish that L-threo-DOPS is also effective when orally administered.

DETD Two hundreds parts by weight of L-threo-DOPS, 167 parts by weight of excipient and 3 parts by weight of lubricant are uniformly mixed with each other. The mixture is then filled up in empty capsules to prepare capsules containing 200 mg of L-threo-DOPS.

DETD Hundred parts by weight of L-threo-DOPS, 168 parts by weight of excipient and 2 parts by weight of lubricant are uniformly mixed with each other. The mixture is then filled up in empty capsules to prepare capsules containing 100 mg of L-threo-DOPS.

DETD According to the present invention, it has been revealed that threo-DOPS exhibits an analgesic activity which is effective for acute pains and chronic or continuous pains. Therefore, threo-DOPS is extremely effective for the treatment of diseases with pains such as postoperative pain, headache, migraine, pains accompanied by rheumatism, post-herpes neuralgia, cancerous pain, pains associated with cervico-omo-brachial syndrome, shoulder periarthritis, spinal distortion, and spondylosis deformans.

IT 3916-18-5
(analgesic activity of)

L12 ANSWER 6 OF 12 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1996318047 EMBASE
TITLE: The effects of the noradrenaline precursor, L-threo-3,4-dihydroxyphenylserine, in children with orthostatic intolerance.
AUTHOR: Tanaka, H. (correspondence); Yamaguchi, H.; Mino, M.
CORPORATE SOURCE: Department of Pediatrics, Osaka Medical College, 2-7 Daigakucho, Takatsuki-shi, Osaka 569, Japan.
SOURCE: Clinical Autonomic Research, (1996) Vol. 6, No. 4, pp. 189-193.
Refs: 16
ISSN: 0959-9851 CODEN: CAURE9
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
007 Pediatrics and Pediatric Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Nov 1996
Last Updated on STN: 6 Nov 1996

SO Clinical Autonomic Research, (1996) Vol. 6, No. 4, pp. 189-193.
Refs: 16
ISSN: 0959-9851 CODEN: CAURE9

CT Medical Descriptors:
adolescent
arterial pressure
article
blood pressure
clinical article
clinical trial

diastolic blood pressure
female
headache: CO, complication
heart rate
human
lassitude: CO, complication
male
oral drug administration
*orthostatic hypotension: DT, drug therapy
school child
standing
supine position
syncope: CO, complication
systolic blood pressure
vertigo: CO, complication
noradrenalin:. . .
RN (noradrenalin) 1407-84-7, 51-41-2; (threo 3,4 dihydroxyphenylserine) 23651-95-8

L12 ANSWER 7 OF 12 ADISCTI COPYRIGHT (C) 2008 Adis Data Information BV on STN
ACCESSION NUMBER: 1996:44047 ADISCTI
DOCUMENT NUMBER: 800436605
TITLE: Analgesic effect of L-threo-3,4-dihydroxyphenylserine (L-DOPS) in patients with chronic pain.
ADIS TITLE: Droxidopa: therapeutic use
Pain
In patients with chronic pain
AUTHOR: Takagi H; Harima A
CORPORATE SOURCE: Institute of Chronic Pain Research, Kyoto, Japan
SOURCE: European Neuropsychopharmacology (Mar 1, 1996), Vol. 6, pp. 43-47
DOCUMENT TYPE: Best Evidence
ADIS REC. CREATED: 17 Apr 1996
RE Pain Control
LANGUAGE: English
WORD COUNT: 369
OTHER SOURCE: ADISINSIGHT 2007000260
ENTRY DATE: Entered STN: 30 Jun 1998
Last Updated on STN: 30 Jun 1998
PD 19960301
TI Analgesic effect of L-threo-3,4-dihydroxyphenylserine (L-DOPS) in patients with chronic pain.
ADIS TITLE: Droxidopa: therapeutic use
Pain
In patients with chronic pain
TX. . . noradrenaline does not cross the blood-brain barrier and therefore has no analgesic effects in mammals. However, a synthetic amino acid, droxidopa [L-threo-3,4-dihydroxyphenylserine, L-DOPS; Sumitomo], acts as a noradrenaline precursor and has been shown to produce naloxone-resistant antinociception in the mouse. This study assessed the analgesic effect of oral administration of droxidopa in patients with chronic pain.
TX. . . (mean 74) years
Sex: 4 male & 14 female
Disease: Pain
Characteristics: patients had chronic pain for > 6 months. Symptoms included: cluster headache (n = 1); central pain after brain infarction (3); spondylosis deformans, low back pain (10); neck-shoulder syndrome (1); postherpetic neuralgia. . .
TX Droxidopa

Drug/Treatment	Dose	Route	Frequency	Duration
Droxidopa	100-300 mg/dose	PO	bid-tid	4-5 weeks

TX Results:

	Placebo (n = 9)	Droxidopa (n = 9)
Mean VAS score (cm)	9.2	4.1 sup(a)
No. of patients with reduced intensity of. . .		8 sup(a)

CT Drug Descriptors: Droxidopa, therapeutic use
CT Disease Descriptors: Pain, treatment

L12 ANSWER 8 OF 12 ADISCTI COPYRIGHT (C) 2008 Adis Data Information BV on STN
ACCESSION NUMBER: 1995:4378 ADISCTI
DOCUMENT NUMBER: 800347428
TITLE: Clinical evaluation of Ro19-6327 (lazabemide hydrochloride) in patients with Parkinson's disease treated L-DOPA: double-blind, placebo-controlled, parallel-group, multicenter comparative study.
ADIS TITLE: Lazabemide + levodopa: therapeutic use Parkinson's disease
AUTHOR: Narabayashi H; Mizuno Y; Yanagisawa N; Ogawa N; Miyatake T; et al.
CORPORATE SOURCE: Juntendo University School of Medicine, Tokyo, Japan
SOURCE: Rinsho Iyaku (Jan 1, 1995), Vol. 11, No. 2, pp. 363-391
ISSN: 0910-8211
DOCUMENT TYPE: Best Evidence
ADIS REC. CREATED: 3 Apr 1995
RE Parkinson's Disease and Movement Disorders
LANGUAGE: Japanese
WORD COUNT: 392
OTHER SOURCE: ADISINSIGHT 1998003552; ADISINSIGHT 2006000619
ENTRY DATE: Entered STN: 30 Jun 1998
Last Updated on STN: 30 Jun 1998
PD 19950101
TX. . . were experiencing motor fluctuations, decreased efficacy or adverse effects.
Concomitant medication: levodopa, anticholinergics (n = 163), amantadine (147), dopaminergic agents (166), droxidopa (65), antihistamines, antidepressants, psychotropics, cerebral metabolism or cerebral circulation improvers, hypotensive and gastro-intestinal medications
SIDE. . . +

	levodopa	levodopa
Total	17 (11.4%)	31 (20.9%)
Nausea	2	7
Dry mouth	1	7
Stomach discomfort	4	4
Headache/heavy headedness	4	2
Dyskinesia	2	0
Dizziness	2	1
Delirium	1	0
Anxiety	1	0

Tremor exacerbation	1	0
Drowsiness. . .		

L12 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:622022 CAPLUS
DOCUMENT NUMBER: 121:222022
ORIGINAL REFERENCE NO.: 121:40189a,40192a
TITLE: Analgesic medicinal composition
INVENTOR(S): Takagi, Hiroshi
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9416689	A1	19940804	WO 1994-JP120	19940128 <--
W: CA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 06227973	A	19940816	JP 1993-34366	19930129 <--
JP 3559572	B2	20040902		
CA 2154455	A1	19940804	CA 1994-2154455	19940128 <--
EP 681838	A1	19951115	EP 1994-905224	19940128 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
US 5616618	A	19970401	US 1995-495480	19950724 <--
PRIORITY APPLN. INFO.:			JP 1993-34366	A 19930129
			WO 1994-JP120	W 19940128

PI WO 9416689 A1 19940804

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9416689	A1	19940804	WO 1994-JP120	19940128 <--
W: CA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 06227973	A	19940816	JP 1993-34366	19930129 <--
JP 3559572	B2	20040902		
CA 2154455	A1	19940804	CA 1994-2154455	19940128 <--
EP 681838	A1	19951115	EP 1994-905224	19940128 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
US 5616618	A	19970401	US 1995-495480	19950724 <--

AB . . . chronic or continuous pain and hence is remarkably efficacious as a remedy for pains and diseases such as postoperative pain, headache, migraine, rheumatic pain, postherpetic neuralgia, cancerous pain, neck-shoulder-arm syndrome, frozen shoulder, spinal sprain and spondylosis deformans. Formulations are given.

IT 3916-18-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic activity of)

L12 ANSWER 10 OF 12 ADISCTI COPYRIGHT (C) 2008 Adis Data Information BV on STN
ACCESSION NUMBER: 1992:50553 ADISCTI
DOCUMENT NUMBER: 800147973
TITLE: Clinical evaluation of selegiline hydrochloride (L-deprenyl) for the therapeutic drug in Parkinson's disease. Double-blind, comparative study in patients

treated between L-dopa combination and L-dopa alone.
ADIS TITLE: Levodopa +- selegiline: therapeutic use
Parkinson's disease
AUTHOR: Takahashi M; Yuasa R; Imai T; Tachibana H; Yorifuji S; et al.
CORPORATE SOURCE: Kinki University School of Medicine, Osaka, Japan
SOURCE: Rinsho Iyaku (Jan 1, 1992), Vol. 8, No. 6, pp. 1411-1453
ISSN: 0910-8211
DOCUMENT TYPE: Best Evidence
ADIS REC. CREATED: 30 Jul 1992
RE Parkinson's Disease and Movement Disorders
LANGUAGE: Japanese
WORD COUNT: 381
OTHER SOURCE: ADISINSIGHT 2000000457; ADISINSIGHT 2002000575; ADISINSIGHT 2006000619
ENTRY DATE: Entered STN: 30 Jun 1998
Last Updated on STN: 30 Jun 1998

PD 19920101
TX. . . 40-75 (mean 62.4) years
Sex: 63 male & 49 female
Disease: Parkinson's-disease
Concomitant medication: bromocriptine (n = 73), amantadine (54), anticholinergic agents (68), droxidopa (18); 106/112 patients received concomitant medication
SIDE. . . (11.7)

anorexia		5 (8.3)
dry mouth		4 (6.7)
dyskinesia		4 (6.7)
orthostatic hypotension		4 (6.7)
headache		3 (5.0)
No. (%) of patients experiencing adverse effects	13 (25.0)	22 (36.7)
No. of patients withdrawn as. . .		

L12 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 1
ACCESSION NUMBER: 1992:164690 BIOSIS
DOCUMENT NUMBER: PREV199293087015; BA93:87015
TITLE: A CASE OF SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE ASSOCIATED WITH DIABETES MELLITUS.
AUTHOR(S): SATO K [Reprint author]; KIMURA T; OTA K; SHOJI M; INOUE M; OHTA M; YAMAMOTO T; CHIBA T; SAEKI S; ET AL
CORPORATE SOURCE: SECOND DEP INTERN MED, TOHOKU UNIV SCH MED, 1-1 SEIRYO-CHO, AOBA-KU, SENDAI 980, JPN
SOURCE: Endocrinologia Japonica, (1991) Vol. 38, No. 3, pp. 331-338.
CODEN: ECJPAE. ISSN: 0013-7219.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 31 Mar 1992
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SO Endocrinologia Japonica, (1991) Vol. 38, No. 3, pp. 331-338.
CODEN: ECJPAE. ISSN: 0013-7219.
AB A 46-year-old man, presenting with headache, nausea, and lassitude, was diagnosed as having diabetes mellitus and hyponatremia, and admitted to Tohoku University Hospital. Insulin treatment improved. . . to an upright posture, accompanied by a fall in blood pressure and a rise

in heart rate. After treatment with droxidopa "a sympathomimetric drug", ambulatory blood pressure gradually increased and hyponatremia disappeared. However, blood pressure and ADH responses to upright posture. . . the baroreceptor reflex stimulated by the postural hypotension, and also by the impaired osmoregulation associated with diabetic neuropathy, and that droxidopa improved cardiovascular function and increased ANP release with resultant urinary dilution and natriuresis in spite of slightly increased ADH release.

IT Miscellaneous Descriptors
HUMAN DROXIDOPA AUTONOMIC-DRUG METABOLIC-DRUG SYMPATHETIC NERVOUS SYSTEM BARORECEPTOR REFLEX ORTHOSTATIC HYPOTENSION OSMOREGULATION

RN 23651-95-8 (DROXIDOPA)

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ACCESSION NUMBER: 1987194691 EMBASE
TITLE: A case with acute pandysautonomia with aseptic meningitis - pathophysiological and therapeutic study.
AUTHOR: Ushiyama, M.; Ikeda, S.-I.; Yazawa, M.; et. al.
CORPORATE SOURCE: Department of Neurology, Shinshu University School of Medicine, Matsumoto, Japan.
SOURCE: Clinical Neurology, (1987) Vol. 27, No. 8, pp. 1035-1042.
ISSN: 0009-918X CODEN: RISHDJ
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
008 Neurology and Neurosurgery
LANGUAGE: Japanese
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991

SO Clinical Neurology, (1987) Vol. 27, No. 8, pp. 1035-1042.
ISSN: 0009-918X CODEN: RISHDJ

AB . . . meningitis, and discuss the pathophysiology and therapy with L-threo-3,4-dihydroxyphenylserine (L-DOPS). The patient was a previously healthy 31-year-old male. He developed headache, abdominal pain, lumbago, and syncope when standing on January 15, 1986. Two days later, high fever, diarrhea and impotence appeared.. . .

RN (threo 3,4 dihydroxyphenylserine) 23651-95-8